Serial No.: 10/069,215

Filed: February 22, 2002

Page : 2 of 14

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Presently amended) The present invention provides a A compound of formula (I), or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof:

$$R^{1}-(Q)_{m}-(CR^{2}R^{3})_{n}-T$$
 $X^{2}-X^{1}$ $N-Z-R^{6}$ $X^{3}-X^{4}$ (I)

wherein

Z is CR⁴R⁵, C(O) or CR⁴R⁵-Z¹, wherein R⁴ and R⁵ are CH₂; Z¹ is C₁₋₄ alkylene, C₂₋₄ alkenylene or C(O)NH;

 R^{+} represents a C_{1} - C_{12} -alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C_{1} - C_{6} -alkoxy, C_{1} - C_{6} -alkylthio, C_{3} -z-cycloalkyl, C_{1} - C_{6} -alkoxycarbonyl and phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_{1} - C_{6} -alkyl, C_{1} - C_{6} -haloalkyl, phenyl(C_{1} - C_{6} -alkyl), C_{1} - C_{6} -alkoxy, C_{1} - C_{6} -haloalkoxy, $S(O)_{2}(C_{1}$ - C_{6} -alkyl), $C(O)NH_{2}$, carboxy or C_{1} - C_{6} -alkoxycarbonyl); or R^{+} represents C_{2} - C_{6} -alkenyl optionally substituted by phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_{1} - C_{6} -alkyl, C_{1} - C_{6} -haloalkyl, phenyl(C_{1} - C_{6} -alkyl), C_{1} - C_{6} -alkoxycarbonyl); or R^{+} represents a 3- to 14-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from: halogen, cyano, nitro, oxo, hydroxyl, C_{1} - C_{8} alkyl, C_{1} - C_{6} hydroxyalkyl, C_{1} - C_{6}

Attorney's Docket No.: 06275-244US1 / A 2214-1P US

Applicant: Stephen Thom et al.

Serial No.: 10/069,215

Filed: February 22, 2002

Page : 3 of 14

haloalkyl, C_{1-G} alkoxy(C_1-C_6 alkyl), C_3-C_7 cycloalkyl(C_1-C_6 alkyl), C_1-C_6 alkylthio(C_1-C_6 alkyl), C_1-C_6 alkyl), C_1-C_6 alkyl), C_1-C_6 alkyl), C_1-C_6 alkyl), aryl(C_1-C_6 alkyl), heterocyclyl(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl), aryl(C_1-C_6 alkyl)S(O_2 , heterocyclyl(C_1-C_6 alkyl)S(O_2 , C_2-C_6 alkenyl, C_1-C_6 alkoxy, carboxy-substituted C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 hydroxyalkoxy, C_1-C_6 alkylcarboxy-substituted C_1-C_6 alkoxy, aryloxy, heterocyclyloxy, C_1-C_6 alkylthio, C_3-C_7 cycloalkyl(C_1-C_6 alkylthio), C_3-C_6 alkynylthio, C_1-C_6 alkylcarbonylamino, C_1-C_6 haloalkylcarbonylamino, $S_3+C_1-C_6$ alkylcarbonylamino, $S_3+C_1-C_6$ alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, oxo, hydroxy, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 haloalkoxy, C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 haloalkoxy, C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, C_1-C_6 alkoxy.

m is 0 - or 1;

Q represents an oxygen or sulphur atom or a group NR^9 , C(O), $C(O)NR^9$, $NR^9C(O)$ or CH-CH; n is 0, 1, 2, 3, 4, 5 or 6 provided that when n is 0, then m is 0;

each R^2 and R^3 independently represents a hydrogen atom or a C_1 - C_4 alkyl group, or $(CR^2R^3)_n$ represents C_3 - C_7 cycloalkyl optionally substituted by C_1 - C_4 alkyl;

T represents a group NR^{10} , $C(O)NR^{10}$, $NR^{11}C(O)NR^{10}$ or $C(O)NR^{10}NR^{11}$, wherin R^{10} is H; X^1 , X^2 , X^3 and X^4 are, independently, CH_2 , CHR^{12} (wherein each R^{12} is, independently, C_1 - C_4 alkyl or C_3 - C_7 cycloalkyl(C_1 - C_4 alkyl)} or C-O; or, when they are CHR^{12} , the R^{12} -groups of X^1 and X^3 or X^4 , or, X^2 and X^3 or X^4 join to form a two or three atom chain which is CH_2CH_2 ; CH_2CH_2 , CH_2OCH_2 or CH_2SCH_2 ; provided always that at least two of X^1 , X^2 , X^3 and X^4 are CH_2 ;

 R^4 and R^5 each independently represent a hydrogen atom or a C_1 - C_4 alkyl group; R^6 is aryl or heterocyclylphenyl, both-optionally substituted by one or more of: halogen, cyano, nitro, oxo, hydroxyl, C_1 - C_8 alkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 haloalkyl, C_{1-6} alkoxy(C_1 - C_6 alkyl), C_3 - C_7 cycloalkyl(C_1 - C_6 alkyl), C_1 - C_6 alkyl), C_1 - C_6 alkyl), C_1 - C_6 alkyl), aryl(C_1 - C_6 alkyl), heterocyclyl(C_1 - C_6 alkyl), arylS(O_2).

Serial No.: 10/069,215

Filed: February 22, 2002

Page : 4 of 14

 C_6 alkyl), heterocyclyl $S(O)_2(C_1-C_6$ alkyl), aryl $(C_1-C_6$ alkyl) $S(O)_2$, heterocyclyl $(C_1-C_6)_2$ alkyl)S(O)₂, C_2 - C_6 alkenyl, C_1 - C_6 alkoxy, carboxy-substituted C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkoxy, C_1 - C_6 alkylcarboxy-substituted C_1 - C_6 alkoxy, aryloxy, heterocyclyloxy, C₁-C₆ alkylthio, C₃-C₇ cycloalkyl(C₁-C₆ alkylthio), C₃-C₆ alkynylthio, C₁-C₆ alkylcarbonylamino, C₁-C₆ haloalkylcarbonylamino, SO₃H, -NR¹⁶R¹⁷, -C(O)NR²¹R²². $S(O)_2NR^{13}R^{14}$, $S(O)_2R^{15}$, $R^{26}C(O)$, carboxyl, C_1 - C_6 alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, nitro, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, phenyl(C_1 - C_6 alkyl), C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $S(O)_2(C_1-C_6 \text{ alkyl})$, $C(O)NH_2$, carboxy or $C_1-C_6 \text{ alkoxycarbonyl}$; R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{13} , R^{14} , R^{16} , R^{17} , R^{18} , R^{19} , R^{21} , R^{22} , R^{23} and R^{24} are, independently hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkyl(C_1 - C_4 alkyl) or phenyl(C_1 - C_6 alkyl); and, R¹⁵ and R²⁰ are, independently, C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, C₂-C₆ cycloalkyl, C₃-C₇ cycloalkyl(C₁-C₄ alkyl) or C₁-C₆ alkyl optionally substituted by phenyl; R²⁵ and R²⁶ are, independently, C₁-C₆ alkyl or phenyl (optionally substituted by one or more of halogen, nitro, cyano, C₁-C₆ alkyl, C₁-C₆ haloalkyl, phenyl(C₁-C₆ alkyl), C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, $S(O)_2(C_1-C_6 \text{ alkyl})$, $C(O)NH_2$, carboxy or $C_1-C_6 \text{ alkoxycarbonyl})$; or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof; provided that when T is C(O)NR¹⁰ and R¹ is optionally substituted phenyl then n is not 0.

2-4. (Cancelled)

- 5. A compound as defined in any one of Examples 1 to 416.
- 6. (Presently amended) A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises:
- (a) when n is at least 1, the CR²R³ group attached directly to T is CHR³ and T is NR¹⁰, reacting a compound of general formula

Attorney's Docket No.: 06275-244US1 / A 2214-1P US

Applicant: Stephen Thom et al.

Serial No.: 10/069,215

Filed: February 22, 2002

Page : 5 of 14

$$R^{1}-(Q)_{m}-(CR^{2}R^{3})_{n}-C \nearrow 0$$

wherein n' is 0 or an integer from 1 to 3 and R¹, R², R³, m and Q are as defined in formula (I), with a compound of general formula

or a salt thereof, wherein X¹, X², X³, X⁴, Z, R⁶ and R¹⁰ are as defined in formula (I), in the presence of a reducing agent; or

(b)—when n is at least 1, the CR²R³ group attached directly to T is C(C₁-C₄-alkyl)₂-and T is NR¹⁰, reacting a compound of general formula

wherein n' is 0 or an integer from 1 to 3, R² and R³ each independently represent a C₁-C₄-alkyl group, and R¹, R², R³, R¹⁰, m and Q are as defined in formula (I), with a compound of general formula

$$O = \begin{array}{c} X^2 - X^1 \\ N - Z - R^6 \\ X^3 - X^4 \end{array}$$

wherein X¹, X², X³, X⁴, Z and R⁶ are as defined in formula (I), in the presence of a reducing agent; or

Attorney's Docket No.: 06275-244US1 / A 2214-1P US

Applicant: Stephen Thom et al.

Serial No.: 10/069,215

Filed: February 22, 2002

Page : 6 of 14

(ea) when T is C(O)NR¹⁰, reacting a compound of general formula

$$R^{1}-(Q)_{m}-(CR^{2}R^{3})_{n}-C < O$$
OH (VI)

wherein R¹, R², R³, Q, m and n are as defined in formula (I), with a compound of formula (III)

$$R^{10}$$
 $X^2 - X^1$ $N - Z - R^6$ (IIII)

wherein X^1 , X^2 , X^3 , X^4 , Z, R^6 and R^{10} are as defined in formula (I), or a salt thereof as defined in (a) above; or

(d) when m is 1 and Q is NR⁹, reacting a compound of general formula (VII), R¹—L¹, wherein L¹-represents a leaving group (e.g. a halogen atom) and R¹ is as defined in formula (I), with a compound of general formula

$$\begin{array}{c|c} X^{2} - X^{1} & X^{2} - X^{1} \\ N + R^{9} - (CR^{2}R^{3})_{n} - T & X^{2} - X^{4} \\ X^{3} - X^{4} & (VIII) \end{array}$$

or a salt thereof, wherein n, T, X¹, X², X³, X⁴, Z, R², R³, R⁶ and R⁹ are as defined in formula (I);

(eb) when at least one of R⁴ and R⁵ represents a hydrogen atom, reacting a compound of general formula

$$R^{1}-(Q)_{m}-(CR^{2}R^{3})_{n}-T$$
 $X^{2}-X^{1}$
 $X^{3}-X^{4}$
 (IX)

Serial No.: 10/069,215

Filed: February 22, 2002

Page : 7 of 14

or a salt thereof, wherein R^1 , R^2 , R^3 , Q, m, n, X^1 , X^2 , X^3 , X^4 and T are as defined in formula (I), with a compound of general formula (X), R^6 - C(O) - R^{20} , wherein R^{20} represents a hydrogen atom or a C_1 - C_4 alkyl group and R^6 is as defined in formula (I), in the presence of a reducing agent; or

(fc) reacting a compound of formula (IX) as defined in (e)(b) above, with a compound of general formula

wherein L^2 represents a leaving group (e.g. a halogen atom) and Z and R^6 are as defined in formula (I); -or

(g) when T is NR¹⁰, reacting a compound of general formula

$$R^{1} (Q)_{m} (CR^{2}R^{3})_{n} - L^{3} (XII)$$

wherein L³-represents a leaving group (e.g. a halogen atom) and R¹, R², R³, m, n and Q are as defined in formula (I), with a compound of formula (III) or a salt thereof as defined in (a) above; or

(h) when T is NHC(O)NR¹⁰, reacting a compound of general formula

$$R^{1}$$
 (Q)_m (CR²R³)_n - N=C=O (XIII)

wherein R¹, R², R³, Q, m and n are as defined in formula (I), with a compound of formula (III) or a salt thereof as defined in (a) above; or

Serial No.: 10/069,215

Filed: February 22, 2002

Page : 8 of 14

(i) when T is C(O)NH, Z is CH₂, n is 1, R² and R³ are hydrogen or C₁-C₄ alkyl and Q is oxygen or sulphur, reacting a compound of formula (XIV):

wherein Hal is a suitable halogen, R², R³, X¹, X², X³, X⁴, Z and R⁶ are as defined in formula (I), with R¹OH or R¹SH in the presence of a suitable base;

and optionally after (a), (b), $\underline{\text{or}}(c)$, $\underline{\text{(d)}}$, $\underline{\text{(e)}}$, $\underline{\text{(f)}}$, $\underline{\text{(g)}}$, $\underline{\text{(h)}}$ or $\underline{\text{(i)}}$ forming a pharmaceutically acceptable salt or solvate of the compound of formula (I) obtained.

- 7. (Presently amended) A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as elaimed in any one of claims claim 1 to 4 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.
- 8. (Presently amended) A process for the preparation of a pharmaceutical composition as claimed in claim 7 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims claim 1 to 4 with a pharmaceutically acceptable adjuvant, diluent or carrier.

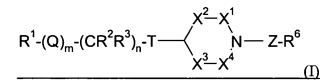
9-10. (Cancelled)

11. (Presently Amended) A method of treating an inflammatory disease asthma in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof, as defined claim 10.

Serial No.: 10/069,215

Filed: February 22, 2002

Page : 9 of 14



wherein

Z is CR⁴R⁵, wherein R⁴ and R⁵ are CH₂;

R¹ represents a 3- to 14-membered saturated or unsaturated ring system which comprises up to two ring carbon atoms that form carbonyl groups and which further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from: halogen, cyano, nitro, oxo, hydroxyl, C₁-C₈ alkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ haloalkyl, C₁₋₆ alkoxy(C₁-C₆ alkyl), C_3 - C_7 cycloalkyl(C_1 - C_6 alkyl), C_1 - C_6 alkylthio(C_1 - C_6 alkyl), C_1 - C_6 alkylcarbonyloxy(C_1 - C_6 alkyl), C_1 - C_6 alkylS(O)₂(C_1 - C_6 alkyl), aryl(C_1 - C_6 alkyl), heterocyclyl(C_1 - C_6 alkyl), $arylS(O)_2(C_1-C_6 alkyl)$, heterocyclyl $S(O)_2(C_1-C_6 alkyl)$, $aryl(C_1-C_6 alkyl)S(O)_2$, heterocyclyl $(C_1-C_6 alkyl)$ C₆ alkyl)S(O)₂, C₂-C₆ alkenyl, C₁-C₆ alkoxy, carboxy-substituted C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ hydroxyalkoxy, C₁-C₆ alkylcarboxy-substituted C₁-C₆ alkoxy, aryloxy, heterocyclyloxy, C₁-C₆ alkylthio, C₃-C₇ cycloalkyl(C₁-C₆ alkylthio), C₃-C₆ alkynylthio, C₁-C₆ alkylcarbonylamino, C₁-C₆ haloalkylcarbonylamino, SO₃H, -NR⁷R⁸, -C(O)NR²³R²⁴, $S(O)_2NR^{18}R^{19}$, $S(O)_2R^{20}$, $R^{25}C(O)$, carboxyl, C_1 - C_6 alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, oxo, hydroxy, nitro, cyano, C₁-C₆ alkyl, C₁-C₆ haloalkyl, phenyl(C₁-C₆ alkyl), C₁-C₆ alkoxy, C_1 - C_6 haloalkoxy, $S(O)_2(C_1$ - C_6 alkyl), $C(O)NH_2$, carboxy or C_1 - C_6 alkoxycarbonyl; m is 0;

n is 2;

each R^2 and R^3 independently represents a hydrogen atom or a C_1 - C_4 alkyl group, or $(CR^2R^3)_n$ represents C_3 - C_7 cycloalkyl optionally substituted by C_1 - C_4 alkyl;

T represents a group C(O)NR¹⁰;

X¹, X², X³ and X⁴ are, independently, CH₂;

R⁴ and R⁵ each independently represent a hydrogen atom or a C₁-C₄ alkyl group;

Serial No.: 10/069,215

Filed: February 22, 2002

Page : 10 of 14

R⁶ is phenyl optionally substituted by one or more of: halogen, cyano, nitro, oxo, hydroxyl, C₁- C_8 alkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 haloalkyl, C_{1-6} alkoxy(C_1 - C_6 alkyl), C_3 - C_7 cycloalkyl(C_1 - C_6 alkyl), C_1 - C_6 alkylthio(C_1 - C_6 alkyl), C_1 - C_6 alkylcarbonyloxy(C_1 - C_6 alkyl), C_1 - C_6 alkylS(O)₂(C_1 - C_6 alkyl), $aryl(C_1-C_6$ alkyl), heterocyclyl(C_1-C_6 alkyl), $arylS(O)_2(C_1-C_6$ alkyl), heterocyclylS(O)₂(C_1 - C_6 alkyl), aryl(C_1 - C_6 alkyl)S(O)₂, heterocyclyl(C_1 - C_6 alkyl)S(O)₂, C_2 - C_6 alkenyl, C₁-C₆ alkoxy, carboxy-substituted C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ hydroxyalkoxy, C₁-C₆ alkylcarboxy-substituted C₁-C₆ alkoxy, aryloxy, heterocyclyloxy, C₁-C₆ alkylthio, C₃-C₇ cycloalkyl(C₁-C₆ alkylthio), C₃-C₆ alkynylthio, C₁-C₆ alkylcarbonylamino, C₁- C_6 haloalkylcarbonylamino, SO_3H , $-NR^{16}R^{17}$, $-C(O)NR^{21}R^{22}$, $S(O)_2NR^{13}R^{14}$, $S(O)_2R^{15}$, $R^{26}C(O)$, carboxyl, C₁-C₆ alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, nitro, cyano, C₁-C₆ alkyl, C_1 - C_6 haloalkyl, phenyl(C_1 - C_6 alkyl), C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $S(O)_2(C_1$ - C_6 alkyl), $C(O)NH_2$, carboxy or C_1 - C_6 alkoxycarbonyl; R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{13} , R^{14} , R^{16} , R^{17} , R^{18} , R^{19} , R^{21} , R^{22} , R^{23} and R^{24} are, independently hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkyl(C_1 - C_4 alkyl) or phenyl(C_1 - C_6 alkyl); and, R¹⁵ and R²⁰ are, independently, C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, C₃-C₆ cycloalkyl, C₃-C₇ cycloalkyl(C₁-C₄ alkyl) or C₁-C₆ alkyl optionally substituted by phenyl; R²⁵ and R²⁶ are, independently, C₁-C₆ alkyl or phenyl (optionally substituted by one or more of halogen, nitro, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, phenyl(C_1 - C_6 alkyl), C_1 - C_6 alkoxy, C_1 - C_6

haloalkoxy, $S(O)_2(C_1-C_6 \text{ alkyl})$, $C(O)NH_2$, carboxy or $C_1-C_6 \text{ alkoxycarbonyl}$.